SYNTHESIS AND CHARACTERIZATION OF TIN, SILICON AND LEAD COMPLEXES WITH BIOLOGICALLY ACTIVE SCHIFF BASES CONTAINING SULPHUR, NITROGEN, OXYGEN DONOR ATOMS

A PROPOSED RESEARCH PLAN IN PARTIAL FULFILLMENT
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Supervisor:

Dr. Har Lal Singh
College of Engineering & Technology

Submitted by:

Mrs. Sunita Bhanuka
Enroll. No. 140300

College of Engineering & Technology
Lakshmangarh, Sikar – 332311 (Rajasthan)

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1. INTRODUCTION

Recent developments in inorganic and organometallic have resulted in a very significantly increased understanding of the bonding structure and reactivity of coordination chemistry. Equally however, the border area between inorganic chemistry and life science should present a challenge to the inorganic chemist to apply his increased understanding in the design of model systems that throw light on behavior of metal ion in biological process and ultimately to look more closely at these process themselves. Coordination chemistry is one of the most active fields of research in the area of inorganic chemistry. The use of coordination compounds as biological probes present as one of the most successful application of the bioinorganic chemistry[1-3]. The transition as well as non transition metallic elements have unparallel tendency to form coordination compounds with Lewis bases. The chemistry of these complexes with Schiff bases continues to attract many researchers, because of their wide applications in food industries, dye industries and in analytical chemistry as well as catalysis and herbicides. These complexes also show higher nematicidal and insecticidal properties.

Coordination chemistry, the chemistry of metal complexes, is one of the most active research areas in inorganic chemistry. The study of coordination chemistry in the modern day context began with two notable scientists Alfred Werner and Sorphus Mads Jorgenson. The pioneering contribution of Werner to the study of coordination chemistry fetched him the Nobel Prize in Chemistry in 1913. Werner's basic ideas on the stereochemistry of metal complexes, mechanism of isomerisation etc. remain unchallenged even today despite all the advanced technical developments which have taken place since his days. However the advent of sophisticated physicochemical techniques of high precision and capability has considerably enriched our understanding of the nature of the metal-ligand bond, the structure and stereochemistry of metal complexes, their stability and other properties. Research has come long way from the time of Werner and Jorgenson, in terms of the growth that the coordination chemistry has experienced over the last few decades. Their work was

a stepping stone for the development of modern inorganic chemistry which is truly a multidisciplinary one in the present day context.

Coordination chemistry encompasses such diverse fields as dyes, nuclear fuels, toxicology, bioinorganic chemistry, medicine, catalysis, material science, ceramics, microelectronics, photonics etc. Industries dealing with organic chemicals, pharmaceuticals, petrochemicals and plastics owe a lot to the findings in the field of coordination chemistry. Nature makes extensive use of coordination compounds and their study is becoming increasingly important in biology as well as in chemistry[1-7]. Many of the biologically active compounds are complexes and even the simpler types of complexes have served as model compounds in investigating bodily process. The living system is partially supported by coordination compounds. Hemoglobin, an iron complex, carries oxygen to animal cells. Myoglobin, chlorophyll and cytochromes are some of the other important complex compounds in living systems. Inorganic compounds particularly metallic ions and complexes are essential cofactors in a variety of enzymes and proteins. The elegance and the variety of the coordination compounds and the intriguing range of concepts that are required to interpret their behaviour have attracted many researchers to the study of their synthesis and to seek an understanding of their chemical reactions. The study of complexes has enabled the inorganic chemists to make significant progress in refining the concept of chemical bonding and to explain the influence that bonding has, on the various properties of the compounds.

Schiff bases have been playing an important part in the development of coordination chemistry. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous (industrial, medicinal and pharmaceutical) scientific areas. It is difficult to cover in this chapter the literature on Schiff base metal complexes, which embraces very wide and diversified subjects comprising vast areas of organometallic compounds and various aspects of bioinorganic chemistry[1,8-10]. Therefore, the introduction part is limited to a brief discussion on the Schiff bases, their metal complexes and general applications of Schiff base complexes with an emphasis on biological applications.

usually interested in synthesizing, isolating, identifying, studying properties and applications of chemical compounds.

3.1. General Objectives

- Develop the skill of independent laboratory work
- Develop experience of how to handle and use chemicals.
- Develop the skill of synthesis, separation (purification) of compounds and then further characterizing those using analytical and spectral methods.
- Acquire knowledge of how to deal with the research or project work

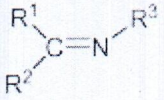
3.2. Specific Objectives

- Designing of new ligands. These ligands are expected to have some unique and unusual features because of variety of size, functional groups and changes of electronic structures.
- Synthesis and purification of biological important ligands and their Sn, Si, and Pb complexes
- Characterization of these compounds by physico-chemical studies such as Elemental analysis, melting point determination, conductance measurements, etc.
- Interpretation of spectroscopic spectra, like IR, NMR, UV, etc.
- Elucidation of structural formula on the basis of interpretation of physiochemical data and theoretical explanations from the literature surveys.
- Screening of the complexes for biological activities such as antibacterial, Antifungal.

4. LITERATURE REVIEW

4.1 Schiff base ligands

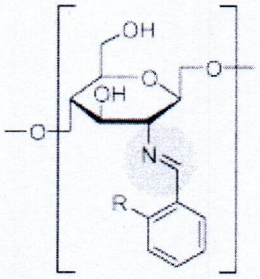
Schiff bases, named after Hugo Schiff [11], are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group.



R^1, R^2, and/or R^3 = alkyl or aryl

Fig. 1.

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers. Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties and imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds (Fig. 2 for some examples). The imine group present in such compounds has been shown to be critical to their biological activities and

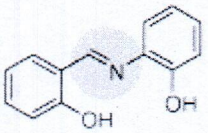


Chitosan-derived Schiff base

[R = H (**2**) or OH (**3**)]

(Antifungal activity)

Natural Product-derived Compound



N-(Salicylidene)-2-hydroxyaniline (**4**)

(Antibacterial activity)

Non-natural Compound

Fig. 2.

In this review we present the general approaches to the synthesis of Schiff bases. We also highlight the most significant examples of compounds belonging to this class, which exhibit antimalarial, antibacterial, antifungal, and/or antiviral activities to have been reported in the literature. The relationship between Schiff bases and other pharmacological activities, such as antiproliferative activities, are not included in this review.

4.2. Schiff Base as Coordinating Ligands

Schiff base ligands coordinate to a metal through the imine nitrogen and another group, usually oxygen, situated on the original aldehyde. When a diamine was first combined with two equivalence of salicylaldehyde, the ligands came into being. The ligands feature two covalent and two coordinate covalent sites situated in a planar array. This makes the ligands ideal for the equatorial coordination of transition metals, leaving the two axial sites open for ancillary ligands. They are very much like porphyrins in this regard, but unlike porphyrins the Schiff base ligands are easy to prepare and are relatively inexpensive. Schiff bases are among the most general N ligands, because the basicity of the sp^2-hybridized N lone pair, although lower than that of amines (sp^3 hybridization), is well suited to form complexes with metal ions. The salicylidene imine group is prone to undergo an acid-catalyzed hydrolysis, reverting to the corresponding salicylaldehyde and diamine in the presence of water. However, the stability of the Schiff base group increases considerably upon coordination with a metal ion and formation of the Schiff base-metal complex. For this reason, in contrast to the free ligand, the Schiff base-metal complex can be used in wet solvents or even in aqueous media without undergoing hydrolysis[12]. Evidence for the tremendous amount of transition-metal chemistry that has been conducted is demonstrated by the fact that the first review in this area was published[13] in 1966. By incorporating additional groups around the phenol portion of the ligand, such as *tert*-Butyl, the ligands can be made highly soluble in aromatic and aliphatic solvents. Incorporation of hydrophilic groups may also lead to ligands that are soluble in water and alcohols[14].

4.3 Applications of Schiff Bases and Their complexes

Schiff bases and their complexes have a wide variety of applications. They are useful in biological field, as anticancer[15], as antitumor[16], as antituberculous[17], as antimalaria[18-19] and also they are found to have clinical, therapeutic[20] and analytical applications[21]. Earlier work has shown that some drugs showed increased activity when administered as metal chelates rather than organic compound[22].

The malleability inherent to the Schiff base ligands has led to their extensive use in transition-metal chemistry, particularly in modeling enzymes and in catalysis[23]. Schiff

bases are suitable ligands for the preparation of libraries due to the easy reaction conditions. Variety of chiral amines and aldehydes are used as precursors to synthesize Schiff bases. Amino acids and peptides are particularly suitable for the creation of effective catalysts. The condensation of aldehyde-bearing coordinating groups with amino acids and peptides provide interesting Schiff bases, used to make a combinatorial library of ligands[24].

4.4. In medicinal chemistry

Many Schiff bases are known to be medicinally important and used to design medicinal compounds[25-28]. It was seen that the biological activity of Schiff bases either increase or decrease upon chelation with metal ions[29-31]. Metal(II) complexes of Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazole and 8-formyl-7-hydroxy-4-methylcoumarin show potent antibacterial activity and antifungal activities[32]. Ru(II)–PPh_3/$AsPh_3$ complexes, containing hydrazone oxime ligands, show considerable activity against selected bacterial species and are capable of binding to Herring sperm DNA in mixed modes[33]. The Cr(III), Fe(III) and Co(III) complexes formed form tetradentate (ONNO) Schiff base ligands, 1,4-bis[3-(2-hydroxy-1-naphthaldimine)propyl]piperazine and 1,8-bis[3-(2-hydroxy-1-naphthaldimine)-menthane, show moderate antimicrobial activity[34] compared to standard antibiotics[35]. The antibacterial activity of the tridentate Schiff base, formed by condensation of 2-amino-3-carboxyethyl-4,5-dimethylthiophene with salicylaldehyde, was found to increase on chelation with transition metal ions[36]. Co(II), Ni(II), Cu(II) and Zn(II) complexes of the Schiff base derived from vanillin and DL-α-aminobutyric acid were also found to exhibit higher antibacterial activity compared to the free Schiff bases[37]. Several mono and binuclear transition metal complexes of the Schiff base derived from phenylaminoacetohydrazide and dibenzoylmethane, are more potent bactericides and fungicides than the ligand[38]. Sharma and Piwnica-Worms reported Schiff base complexes that target hemozoin aggregation like the antimalarial drug, chloroquine[39-41].

Investigations on the interactions of DNA with transition metal complexes provide leads for rational drug design, as well as means for the development of sensitive chemical probes for DNA[42,43]. These interactions would be either covalent or non-covalent. In covalent binding the labile part of the complexes is replaced by a nitrogen base of DNA.

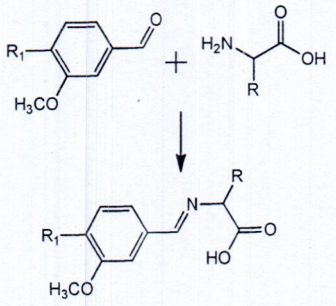
On the other hand, the non-covalent DNA interactions include intercalative, electrostatic and groove binding of cationic metal complexes along periphery of the DNA helix, the major or minor groove. Intercalation involves the partial insertion of aromatic heterocyclic rings between the DNA base pairs.

5. Work Plan & Methodology:

In order to achieve the objectives mentioned above the present study would be carried out in the following phases, keeping the above background knowledge in view:

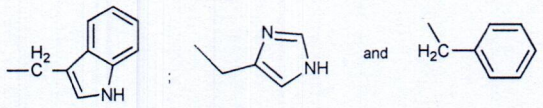
a. Synthesis of New Schiff Base Ligands

(i) Synthesis of Oxygen and Nitrogen donor ligands:

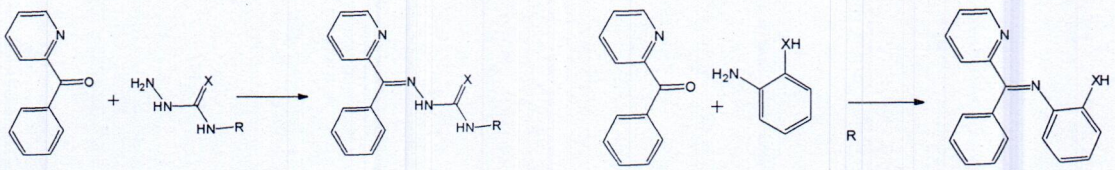


R_1 = H and OCH_3

R = $-CH_3$; $-CH(CH_3)_2$; $-CH_2SH$; $-CH_2OH$; $-(CH_2)_2SCH_3$;



(ii) Synthesis of Sulfur, Oxygen and Nitrogen donor ligands:



X= O and S

R = H and C_6H_5

X= O and S

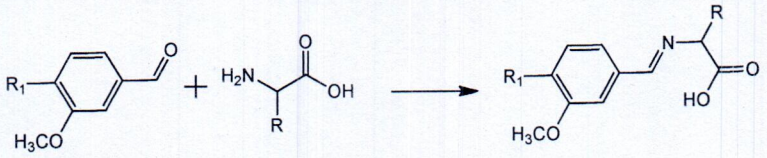
b. Starting materials of Tin, Lead, and Silicon will be synthesized or purchased. Synthesis of metal precursors, if not available commercially.
c. Synthesis of metal complexes involving various Schiff bases
d. Characterization of complexes by analytical and Spectroscopic technique.
e. DFT calculations will be carried out and optimized geometries of the complexes.
f. Screening of Antimicrobial activity.

Year wise Plan of research work

Autumn Semester 2014-15	Completed required Course Work
Spring Semester 2014-15	Review of Literature Synthesis of 20 New Schiff base of Ligands (Oxygen and Nitrogen donor atoms)
Autumn Semester 2015-16	Synthesis of Pb(II) Complexes with Schiff base of Ligands (Oxygen and Nitrogen donor atoms)
Spring Semester 2015-16	Synthesis and characterization of tin and silicon Complexes with Schiff base of Ligands (Oxygen and Nitrogen donor atoms)
Autumn Semester 2016-17	Synthesis of New Schiff base of Ligands (Sulphur, Oxygen and Nitrogen donor atoms) Synthesis of lead and tin Complexes with Schiff base of Ligands (Oxygen and Nitrogen donor atoms)
Spring Semester 2016-17	Synthesis of silicon Complexes with Schiff base (sulphur, Oxygen and Nitrogen donor atoms) Writing of thesis

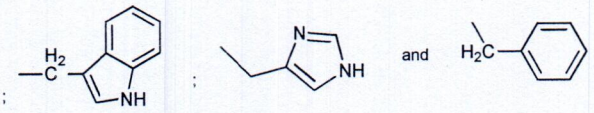
6. WORK ALREADY DONE

Synthesis of a new series of Schiff base having nitrogen and oxygen donor atoms



R_1 = H and OCH_3

R = $-CH_3$; $-CH(CH_3)_2$; $-CH_2SH$; $-CH_2OH$; $-(CH_2)_2SCH_3$;



Synthesis of Lead(II) complexes

$$Pb(OOCCH_3)_2 + 2\overset{\frown}{N\ O}H \xrightarrow[\text{reflux 6-8 h.}]{\text{benzene + methanol}} Pb(\overset{\frown}{N\ O})_2 + 2CH_3COOH$$

where $\overset{\frown}{N\ O}H$ represents the donor system of the Schiff bases

Publication: Published two research papers in International Journals

1. Synthesis, Spectroscopic characterization, biological screening and theoretical studies of organotin(IV) complexes of semicarbazone and thiosemicarbazones derived from (2-hydroxyphenyl)(pyrrolidin-1-yl)methanone, *Research On Chemical Intermediates, 2015, by Springer.*

2. Synthesis, Spectral, Characterization, DFT and antimicrobial studies of tin(II) and lead(II) complexes with semicarbazone and thiosemicarbazones derived from (2-hydroxyphenyl)(pyrrolidin-1-yl)methanone, *Journal of Coordination Chemistry,* Accepted, October, 2015, by Taylor & Francis .

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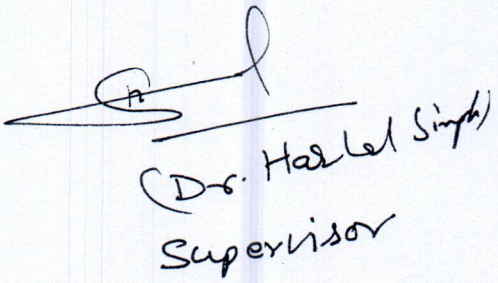
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